Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 63, 68-76, 78-88, 94, 97-116, 118-123, 126 and 128-139 are pending in the application, with claim 63 being the sole independent claim. Claims 74, 99, 105-107, 111-113, 121-123 and 133 have been withdrawn from consideration by the Examiner. Claims 1-62, 64-67, 77, 89-93, 95, 96, 117, 124, 125 and 127 have been canceled without prejudice or disclaimer.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated February 4, 2009, the Examiner has made one rejection of the claims. Applicants respectfully offer the following remarks concerning this element of the Office Action.

III. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at page 2 and in view of Applicant's amendment, the Examiner has withdrawn the previous rejection of claims 63, 68-73, 75, 76, 78-88, 94, 97, 98, 100-104, 108-110, 114-116, 118-120, 124, 126, 128-132 under 35 U.S.C. § 103(a) as being unpatentable over Stockley *et al.* (US Patent 6,159,728;

hereinafter "Stockley") in view of Deghenghi *et al.* (US 2002/0187938; hereinafter "Deghenghi") and further in view of Kojima *et al.* (Nature, 1999 Vol. 402, p. 656-660; hereinafter "Kojima") and Maita *et al.* (Gen Pept Accession VCBPQB, 1971; hereinafter "Maita"). Applicants gratefully acknowledge the withdrawal of this rejection.

However, in the Office Action at pages 3 and 4, the Examiner has newly rejected claims 63, 68-73, 75, 76, 78-88, 94, 97, 98, 100-104, 108-110, 114-116, 118-120, 124, 126, 128-132 and 134-139 under 35 U.S.C. § 103(a) as being unpatentable over Stockley in view of Deghenghi, Kojima and Maita, and further in view of Nielsen *et al.* (US Patent 6,548,651 B1, hereinafter "Nielsen"). Applicants respectfully traverse this rejection.

The presently claimed invention provides for compositions wherein ghrelin or ghrelin peptides are bound to virus-like-particles (VLPs) and subunits of VLPs, respectively, leading to highly ordered and repetitive conjugates representing potent immunogens for the induction of immune responses against ghrelin, in particular of high titers of anti-ghrelin antibodies (*see* paragraphs [0012]-[0018] of the published application, US 2004/0076645 A1).

Applicants respectfully submit that the references cited by the Examiner in making the present obviousness rejection, viewed alone or in combination, neither disclose nor suggest all of the elements of the present claims. In particular, the cited references do not disclose or suggest a composition comprising a virus-like particle with at least one first attachment site "*wherein said first attachment site is*

a lysine residue of said virus-like particle and said second attachment site is a cysteine residue" as recited in the present claims.

Applicants respectfully assert that the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving *Graham* inquiries has been emphasized by the Office within its published Examination Guidelines. *See* "Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc"., *Fed. Reg.* 72:57526- 57535 (October 10, 2007), hereinafter "Examination Guidelines." Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination disclose all of the elements of the claims in its proper function, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result. In the present case, this burden has not been met.

Moreover, to establish a *prima facie* case of obviousness involving structurally similar compounds, the Examiner must provide a showing that there is adequate support in the prior art for the changing the structure of a compound

disclosed in the primary reference. *See Takeda Chem. Inds. v. Alphapharm*, 492 F.3d 1350, at 1356 (2007), citing *In re Grabiak*, 769 F.2d 729, at 731-732 (Fed. Cir. 1985). There is also the additional requirement that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention," *Takeda* at 1356, citing *In re Jones*, 958 F.2d 347 (Fed. Cir.1992); *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990); *Grabiak* at 729; *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984). Thus, *Takeda* mandates that a *prima facie* case of obviousness requires the identification of a lead compound in the primary reference, followed by a clear articulation of the reasons why the artisan would change the compound in a particular way to achieve a predictable result.

As the Examiner concedes, Stockley does *not* disclose the association of non-peptide covalent bonds of *lysine residues of virus-like particles of an RNA-bacteriophage* as first attachment sites with *cysteine residues of the ghrelin antigens* as second attachment sites forming highly ordered and repetitive ghrelin arrays representing for the induction of immune responses against ghrelin. Accordingly, Stockley is seriously deficient as a primary reference upon which to attempt to base a *prima facie* case of obviousness.

Moreover, neither Deghenghi nor Kojima or Maita disclose compositions comprising a virus-like particle of an RNA-bacteriophage with at least one first attachment site and ghrelin or ghrelin peptides as antigens or antigenic determinants with at least one second attachment site, wherein *said first attachment site is a lysine residue of said virus-like particle and wherein said*

second attachment is a cysteine residue, as, *inter alia*, required by the present claims.

In making the new obviousness rejection using Nielsen as a further reference, the Examiner contends that Nielsen discloses a "non-peptide heterobifunctional cross-linker succinimidyl 6-(β-maleimido-propionamido) hexanoate (SMPH) covalently linking peptides with nucleic acid molecules representing bacterial antigens through either a cysteine (C) or a lysine (K) residue." *See* Office Action at page 3.

The Examiner further contends that:

> It would have been *prima facie* obvious to the person of ordinary skill in the art to covalently attach Stockley's RNA Qβ bacteriophage to Deghenghi's and/or Kojima's ghrelin peptide using Nielsen's non-peptide heterobifunctional cross-linker succinimidyl 6-(β-maleimido-propionamido) hexanoate (SMPH) capable of reacting with the first attachment site which is a lysine residue and a second attachment site which is a cysteine residue because Nielsen teaches that the SMPH is a suitable linker for attachment of peptides with nucleic acids.

Office Action at pages 3 and 4. (Emphasis added). Applicants respectfully disagree with the Examiner's assertions and contentions.

The disclosure of Nielsen relates to peptide nucleic acid (PNA) sequences that are modified in order to obtain PNA molecules which exhibit anti-infective properties. *See* Nielsen column 1, lines 26-29. Specifically, Nielsen discloses that the PNA molecules are modified by linkage to a peptide or peptide-like sequence that enhances the activity of the PNA. Nielsen further discloses that the PNA molecule may be connected to the peptide moiety either by direct binding or by a linker. *See,* Nielsen column 7, lines 66-67. In the instances where a linker is

used, the linker may be used as a single linking group or together with more groups, and different linking groups can be combined in any order and number. *See,* Nielsen at column 8, lines 21-25. Finally, Nielsen discloses that the peptide may be linked to the PNA sequence via either the amino or carboxy end, an internal part of the peptide, or alternatively, both the amino and carboxy ends. *See,* Nielsen at column 8, lines 42-46. Nielsen discloses that the modified PNA molecules form "a pattern comprising positively charged and lipophilic amino acids or amino acid analogues." *See,* Nielsen at column 3, lines 53-55.

In contrast to Nielsen, the presently claimed invention provides compositions comprising a virus-like particle of an RNA-bacteriophage to which ghrelin antigens are associated through specific non-peptide covalent bonds, and wherein said association is effected by way of *lysine residues of virus-like particles of an RNA-bacteriophage* and *cysteine residues of the ghrelin antigens* as second attachment sites. The specific attachments of the ghrelin antigens by way of cysteine residues to lysine residues of the virus-like particle of an RNA-bacteriophage result in highly ordered and repetitive ghrelin arrays that represent potent immunogens for the induction of immune responses against ghrelin. *See*, the present specification at paragraphs [0183] - [0188].

As outlined above, there is no disclosure in Nielsen that would have led the skilled artisan to modify the structure of Stockley in order to prepare the compositions of the presently claimed invention. Thus, the Examiner's contention that "SMPH is a suitable linker for attachment of peptides with nucleic acids" is insufficient to cure the deficiencies of Stockley, Deghenghi, Kojima and Maita.

In making the new rejection using Nielsen as further reference, the Examiner asserts that:

> One would have been motivated to use Nielsen's succinimidyl 6-(β-maleimido-propionamido) hexanoate (SMPH) linker to attach Deghenghi's and/or Kojima's ghrelin peptide to Stockley's RNA Qβ bacteriophage because Nielsen teaches that the SMPH linker is used to attach peptides and nucleic acid molecules together.

The Examiner further contends:

> One would have had a reasonable expectation of success to attach Deghenghi's and/or Kojima's ghrelin peptide to Stockley's RNA Qβ bacteriophage using Nielsen's SMPH linker because the linker technology has been well established in the art at the time of the present invention as evidenced by Nielsen et al.

Office Action at page 4, second and third paragraphs. (Emphasis added). Applicants respectfully disagree with these statements.

In contrast to the Examiner's contentions and assertions, Nielsen does not disclose or suggest *lysine residues of virus-like particles of an RNA-bacteriophage* as first attachment sites to associate through non-peptide covalent bonds with *cysteine residues of the ghrelin antigens* as second attachment sites. To the contrary, the disclosure of Nielsen provides no guidance to one of ordinary skill in the art as to *how* to obtain the specific attachments of the ghrelin antigens, by way of cysteine residues on the ghrelin antigens to lysine residues of the virus-like particle of an RNA-bacteriophage, thereby resulting in highly ordered and repetitive ghrelin arrays. As indicated above, Nielsen discloses PNA molecules which are either directly or *optionally* associated via a linker to a peptide. Moreover, when a linker is used, the linkers disclosed in Nielsen may be used

either as a single linking group or as a combination of multiple linking groups. Furthermore, the PNA molecule binds at various positions along the peptide molecule, giving rise to *various* PNA molecule-peptide patterns in the Nielsen constructs, whereas the ghrelin array patterns of the presently claimed invention are highly ordered and repetitive due to the specific attachments sites within the compositions of the presently claimed invention.

Thus, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to use the linker construct of Nielsen to attach the ghrelin peptide of Deghenghi and/or Kojima to the RNA Qβ bacteriophage disclosed in Stockley, as such a modification is neither disclosed nor suggested in any of the cited references. Moreover, even if such a modification was disclosed or suggested in these references, such a combination still would not have produced the compositions of the presently claimed invention, and in particular, the specific attachments of the ghrelin antigens by way of cysteine residues to lysine residues of the virus-like particle of an RNA-bacteriophage resulting in highly ordered and repetitive ghrelin arrays as recited in the present claims.

Additionally, Applicants respectfully submit that the Examiner is mistaken in the contention that one would have a reasonable expectation of success as the disclosures of Stockley, Deghenghi, Kojima, Maita and Nielsen would *not* yield the compositions of the present invention. As indicated above, Nielsen discloses various patterns of positively charged and lipophilic peptides or peptide analogues which are linked in various manners, *i.e.*, either directly or *optionally via a linker*, to PNA molecules in order to obtain novel PNA molecules with enhanced anti-

infective properties. Thus, Applicants respectfully submit that such a disclosure would not have led a person skilled in the art to prepare compositions of the presently claimed invention that are formed by association through non-peptide covalent bonds of *lysine residues of virus-like particles of an RNA-bacteriophage* as first attachment sites with *cysteine residues of the ghrelin antigens* as second attachment sites. Moreover, a person skilled in the art would not have been led to prepare the highly ordered and repetitive ghrelin arrays of the presently claimed invention that induce an immune response against ghrelin.

Finally, Applicants respectfully submit that the Examiner's assertions are based on impermissible hindsight. *See* M.P.E.P. § 2145(X)(A). As the Federal Circuit has held numerous times, such a hindsight-based analysis is impermissible. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.").

In *KSR Int'l Co v. Teleflex Inc.*, the Supreme Court also cautioned against the use of hindsight in support of an obviousness rejection. *See* 127 S.Ct. 1727, 1742 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant on *ex post* reasoning."). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Nielsen cannot and does not cure the deficiencies of Stockley, Deghenghi, Kojima, and Maita. Thus, the cited references cannot be properly combined in an attempt to make out a *prima facie* case of obviousness of the presently claimed invention. Therefore, Applicants respectfully assert that the present claims would not have been obvious over Stockley, Deghenghi, Kojima, Maita and Nielsen alone or in combination. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over these references is respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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